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Purpose: To determine the value of small-field-of-view 2-D and 3-D digital mammography in the evaluation of breast calcifications.
Materials and Method: In our preliminary work, we have compared the appearance of clustered calcifications in film-screen mammograms, digital 2-D mammograms and digital 3-D images. Three radiologists have separately reviewed each modality for each case. The radiologists rated each case as: 5 = definitely malignant, 4 = probably malignant, 3 =indeterminate, 2 = probably benign, and 1 = definitely benign. A score of 3 or higher indicated a biopsy was necessary.
Results: Wehave found that the diagnostic accuracy increased from 36% to 77% with the addition of 2-D and 3-D digital images. In no case, was a malignant calcification cluster downgraded below a score of 3, so that there was never a case where a biopsy would not have been performed on a malignant cluster.
Conclusion: 2-D and 3-D digital images of breast calcifications provide greater diagnostic specificity and thus may help reduce the number of unnecessary biopsies.

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Emily Cant MD 2/22/98

PI - Signature Date

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ANNUAL REPORT FOR GRANT DAMD17-96-1-6280

Principal Investigator: Emily F. Conant, M.D.

INTRODUCTION

Breast calcifications detected mammographically and considered indeterminate or suspicious, account for 50% of biopsies for mammographically detected nonpalpable lesions. The positive predictive value (PPV) of film screen mammography (FSMAM) in determining the malignant nature of calcifications is also low (approximately 30%) (Conant, et al, 1994) (Homer, 1992). We have developed a readily implementable technology that we believe will reduce the number of false positive breast biopsies of calcifications. Our technique of combining two-dimensional (2-D) and novel three-dimensional digital mammographic (3-D DMAM) analysis of breast calcifications allows the analysis of the 3-D morphology of individual calcifications as well as the 3-D spacial orientation of a cluster of calcifications in breast tissue.

Background and Preliminary Studies:

The low specificity of traditional film screen mammography (FSMAM) in evaluating breast calcifications is due to many factors. Many of the calcific particles seen microscopically after a biopsy is performed are below the resolution of the present FSMAM imaging system. In addition, the 3-D characteristics of individual calcifications and of calcifications within a cluster are difficult to assess by the two-dimensional (2-D) images of FSMAM.

The digital mammographic analysis of calcifications has several advantages over the FSMAM evaluation. With direct digital imaging, there is a significantly improvement in the signal-to-noise (SNR) of the resultant image. In addition, FSMAM images suffer from several other limitations including limited latitude that reduces contrast and film granularity noise which reduces the SNR of the image. These limitations are particularly significant at the high spatial frequencies required for FSMAM to record calcifications (Maidment 1993, Maidment 1993a). The digital mammographic system has a limited spatial resolution of 50 μm but a contrast resolution 3x greater than FSMAM.

Since with traditional FSMAM, the film serves as both the image detector and display device, there is no ability to enhance images after acquisition to improve the low contrast resolution inherent in film screen systems. In a digital system, the digital detector functions separately from the acquisition computer which quantifies the image for display on a separate monitor. The separation of these 3 components allows manipulation of each aspect of the image production thus providing more control over the final image. Subtle areas of contrast difference in the 2-D DMAM image may be enhanced or magnified to improve image quality and resolution. This post-acquisition image processing may increase the conspicuity of calcifications and allow better differentiation between benign and malignant lesions.

BODY

EXPERIMENTAL METHODS

Film Screen Imaging

Women undergoing breast biopsies for nonpalpable calcified breast lesions were invited to be included in the study. The film screen mammographic images used for the study included any additional mammographic views (spot magnification etc.) deemed necessary for the diagnostic work-up. IRB and informed consent were obtained from all patients prior to the digital mammographic imaging.

Digital Imaging Procedure

We acquire digital mammographic images (DMAM) using the commercially available Fischer Mammotest™ prone breast biopsy imaging system fitted with a Fisher Mammovision™ Digital Mammography Image Detector. The three-dimensional digital mammographic (3-D DMAM) images are acquired from three 15 degree divergent angle images obtained using the Fischer Mammotest™ stereotactic digital imaging system. These images are analyzed using a novel computer algorithm which reconstructs the morphology of each calcification within a cluster as well as the 3-D arrangement of the calcifications in the cluster. Our software which identifies, segments and reconstructs allows the rendering of the 3-D morphology of individual calcifications and the 3-D arrangement of calcifications within a cluster. The steps for 3-D reconstruction are outlined below:

Step 2. Segmentation

To segment each individual calcifications from the background, a seed point is entered manually. The seed point and standard deviation of an area surrounding the seed point are calculated. A recursive region-growing algorithm is then applied to segment all adjoining pixels whose value are within 1.4 standard deviations of the mean. This first step results in the production of a set of binary images of the calcifications viewed at different angles. (Figure 1)

Step 3. Correlation

The calcifications in each of the stereo images are identified manually .The corresponding image of the calcification is identified in each view, and those images are also segmented. These steps are repeated for every calcification for which correspondence between the views is found. The projected images of each calcification are matched in the different views from the positions, shapes and sizes of the projected images. (Figure 2)

Step 4. Reconstruction

The *3-D location* of each calcification is determined geometrically by comparing the x, y, z location in each of the stereo views (figure 1). Determination of the *3-D shape* is performed using the segmented image data in conjunction with a simulated annealing reconstruction method (figures 2 and 3). The intensity of the signal in each pixel of each view is dependent upon the amount of calcific material in the path of the x-rays that contribute to that pixel.

Step 5. Image Analysis (Figure 4)

For each case, three radiologists separately reviewed the images from each imaging modality. The radiologists rated each case using a modified BIRADs scale:

1= definitely benign
2= probably benign
3= indeterminate
4= probably malignant
5= definitely malignant

A score of 3 or higher indicates a biopsy was recommended. The ratings from each radiologist were collapsed into one observation per calcification case. This was performed by taking the majority reading of at least two of the three readers to reach a single numerical rating for each case.

STATISTICAL ANALYSIS

Since only women who had a positive FSMAM where enrolled in our study, we are unable to calculate sensitivity for FSMAM. Since our reading were performed by consensus, we are able to report a specificity for each imaging modality defined as

$$\text{Specificity} = \frac{TN}{TN+FP}$$ (Hennekens and Buring, 1987)

Accuracy will be determined for the FSMAM study, the combination of FSMAM and 2-D DMAM, and the combination of FSMAM, 2-D DMAM and 3-D DMAM. Accuracy will be defined as

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN}$$ (Hennekens and Buring, 1987)

The measures of specificity and accuracy will however, be limited since the cases were all destined to biopsy. This selection of cases significantly impacts on the measure of specificity and accuracy for FSMAM since the number of FSMAM true negative (TN) cases is ineffect zero since all cases were recommended for biopsy. These measures will therefore be most useful as a comparison between the modalities, i.e., the improvement if any in the specificity and accuracy gained by each additional modality compared to FSMAM alone.

RESULTS

Thus far 66 cases of calcifications have been obtained. Of these, 44 have been reviewed and graded completely. The results of these 44 are presented .

Of the 44 cases, all were recommended for biopsy based on suspicious calcifications seen on the initial FSMAM study. On histologic review, 30 (68%) were due to benign processes, 14 (32%) were due to malignant lesions. This ratio of benign to malignant is similar to the ratio or positive predictive value (approximately 36%) for biopsies performed for non palpable lesions at our hospital. (The process of re-reviewing the cases actually resulted in the downgrading of one FSMAM case so that no biopsy would have been recommended.)

Of the **benign** cases (n=30), 12 were downgraded so that no biopsy would have been recommended if 2-D DMAM analysis had been included. An additional 6 cases were downgraded so that no biopsy would have been recommended if both 2-D and 3-D DMAM images were analyzed. This addition of 2-D and 3-D DMAM analysis would have resulted in a 41% reduction in benign biopsies.

Of the **malignant** cases (n=14), no cases were downgraded so that a biopsy was not recommended but four cases were upgraded when both 2-D DMAM and 3-D DMAM images were included. This upgrading is reflected in the improvement in diagnostic specificity and accuracy.

<u>Accuracy</u>

Accuracy of FSMAM= 36.4%
Accuracy of FSMAM+2-D DMAM= 63.6%
Accuracy of FSMAM+2-D DMAM+3-D DMAM= 77.3%

<u>Specificity</u>

Specificity of FSMAM= 6.7%
Specificity of FSMAM+2-D DMAM= 46.7%
Specificity of FSMAM+ 2-D DMAM+3-D DMAM= 66.7%

DISCUSSION AND RECOMMENDATIONS

With the additional information gained from the direct digital imaging, we have shown a significant improvement in diagnostic accuracy. In instances where calcifications are associated with a mass density, we can distinguish preferentially peripherally distributed calcifications from homogeneously distributed calcifications. Peripheral calcification are most frequently associated with a benign process. The spacial orientation of calcifications within a small cluster can be quite difficult to perceive using conventional FSMAM and its 2-D projections. We have also been able to elucidate the linear distribution of calcifications contained in a ductal system, a sign highly predictive of carcinoma.

The improvements in contrast resolution and in the signal-to-noise ratio of the direct digital system has improved the conspicuity of breast calcifications. The ability to enhance the contrast in areas of dense breast glandularity after image acquisition is directly responsible for the improvements in specificity and accuracy of the 2-D DMAM over the FSMAM. The greatest improvement in accuracy and specificity comes with the improved contrast resolution seen with 2-D DMAM. There is a second smaller gain obtained with the digital 3-D imaging.

At this point, the 3-D imaging performed for this grant is dependent on manual segmentation and correlation. A second Department of Defense grant (P.I. is Andrew Maidment) supporting research to automate this portion of the 3-D reconstruction is ongoing. Until the software is designed to automate this function, the use of 3-D reconstruction for evaluating breast calcifications is much to time consuming to be clinically practical.

We are encouraged with the data obtained from our first set of 44 cases analyzed but have temporarily stopped accruing additional cases and have not analyzed the other 22 that we have accrued. As the Principal Investigator of this grant, I have relocated to the University of Pennsylvania (same city!) and am now negotiating a subcontract to complete the study. While working out this negotiation, we have put a hold on all grant funds. Andrew Maidment Ph.D., will become the new P.I. since he remains at the originally funded institution. We look forward to completing the work collaborating between the two institutions, the University of Pennsylvania and Thomas Jefferson University.

CONCLUSIONS

Clinically, the significance of our novel imaging techniques is that we have the potential of decreasing the number of "false positive" biopsy recommendations given for indeterminate FSMAM findings. With the additional information gained from the 2-D and 3-D DMAM, we could reduced the number of these unnecessary biopsies significantly. In our representative series, 63.6% of biopsies performed for non palpable lesions were benign. With the addition of our digital imaging this was reduced to only 22.7%. These unnecessary breast biopsies are physically and psychologically traumatic as well as costly.

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Maidment ADA, Yaffe MJ, Plewes DB, et al. Imaging performance of a prototype scanned-slot digital mammography system in: Medical Imaging VII. Physics of Medical Imaging. Proceedings of the SPIE 1896:93-103.

Hennekens CH, Buring JE. Screening in: Epidemiology in Medicine, Boston, Little Brown, (p) 331.

APPENDIX

The following published articles and abstracts were supported by the U.S. Army Medical Research and Materiel Command under #DAMD17-96-1-6280:

1. Maidment ADA, Conant EF, Feig SA, Piccoli CW, Albert W. Three-dimensional analysis of breast calcifications. Proceedings of the 3rd International Digital Mammography Meeting New York, NY, June, 1996 (in) Doe D ed: Digital Mammography. Elsivier, NY 1996.

2. Maidment ADA, Conant EF, Feig SA. 3-D Imaging of Mammary Calcifications. Reconstruction from a limited number of digital mammograms. Proceedings of IEEE International Conference on Image Processing, Philadelphia, PA, July 1996. Med Phys 23 (6) 1106-1107, 1996.

3. Maidment ADA, Albert M, Conant EF, Feig SA. 3-D mammary calcification reconstruction from a limited number of views. Proceedings SPIE, Vol 2708, Physics of Medical Imaging, February 1996.

4. Conant EF, Maidment ADA, Albert M, Piccoli CW, Nussbaum SA, McCue PA. Small field of view digital imaging of breast calcifications: A method to improve diagnostic specificity. Radiology 1996; 201:369.

5. Conant EF, Maidment ADA, Albert M, Feig SA, McCue PA. 2-D and 3-D digital imaging of breast calcifications: A method to improve diagnostic specificity. Radiology 1996; 201:448.

6. Maidment ADA, Albert M, Conant EF, Piccoli CW, McCue PA. Prototype workstation for 3-D diagnosis of breast calcifications. Scientific Exhibit. Radiology 1996; 201:556.

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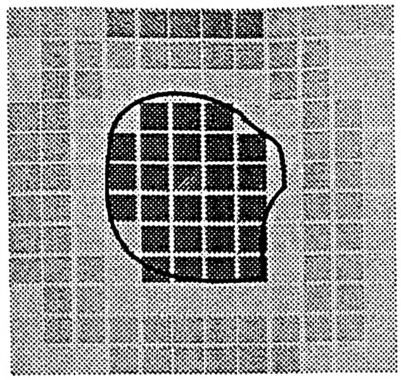
8. Maidment ADA, Albert M, Conant EF, Feig SA, Piccoli SW, Nussbaum SA, et al. a computer workstation for 3-D imaging of the breast. Radiology 1997; 205:803.

9. Conant EF, Maidment ADA, Albert M. 2-D and 3-D digital imaging of breast calcifications: A method to improve the diagnostic specificity of mammography. Proceeding, Vol 1, (p) 101. The Department of Defense Breast Cancer Research Program Meeting, Era of Hope, Nov 1997.

PERSONNEL

Emily F. Conant, MD	Principal Investigator	Radiologist
Andrew Maidment, PhD	Co-investigator	Physicist (to become P.I.)
Catherine Piccoli, MD	Co-investigator	Radiologist
Michael Albert, PhD	Co-investigator	Computer Programmer
Anna Vincent, RTM	Technologist	
Karen White	Statistician	



1) Choose a seed point

2) Determine Mean (M) and Standard Deviation (σ)

3) Select cells which are connected and satisfy:

$$M - P_{ij} > 1.4\,\sigma$$

4) Determine background area

Figure 1. Illustration of a calcification (shown in outline), as well as the segmented area of the calcification (dark grey), the seed point for the segmentation (the triangle) and the area used to estimate the background (medium grey). The algorithm used to segment the calcification is shown above. A seed point is entered manually. The mean and standard deviation of an area surrounding the seed point are calculated. a recursive algorithm is then applied to segment all adjoining pixels whose value $(P)_{ij}$ are within 1 to 2 standard deviations (σ) of the mean (M). The background region is fitted in a least squares sense to a 2-D plane. This plane is used to determine an estimate of the background pixel values in the area of calcifications.

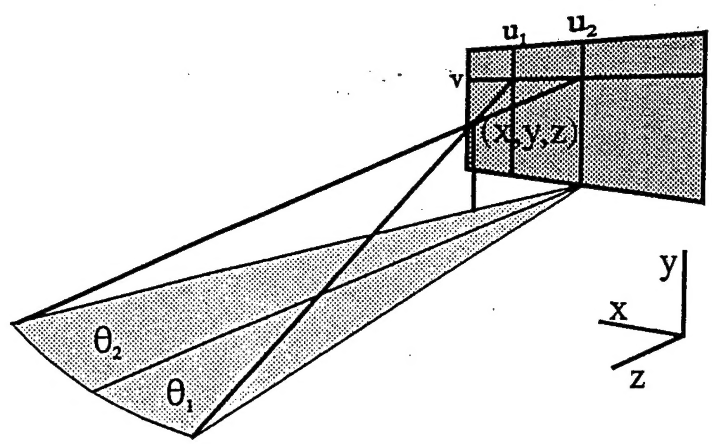


Figure 2. Geometry used in acquiring 3-D images. An object (x,y,z is imaged with the x-ray tube at point 1, yielding a projection at (u_1, v). When the x-ray tube is at point 2, the object is projected to (u_2, v).

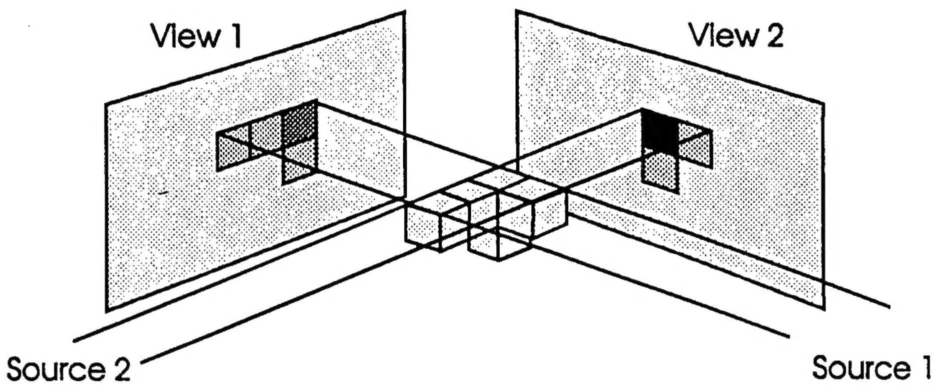


Figure 3. A simplified illustration of the reconstruction method is shown using two views. The object is treated as a set of voxels bounded by the region defined by the intersection of the back-projections of the images. The attenuation coefficient of each voxel is representative of either air or calcific material. The intensity in each image (view) is dependent upon the thickness of material in each projection through the object. Reconstruction is performed by simulating the attenuation of x-rays in a computer model, and then modifying the model such that the attenuation produced by the simulated calcifications matches that of the actual projections.

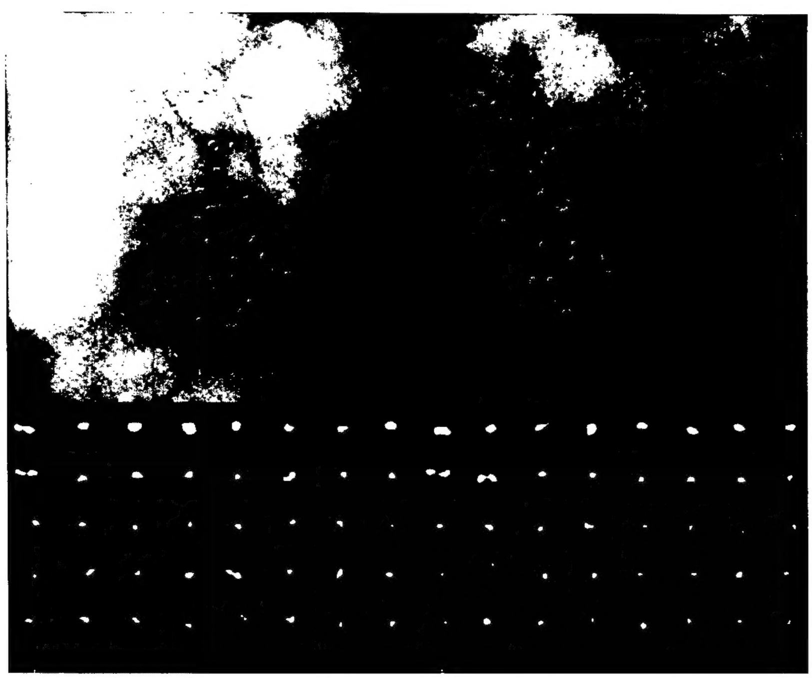


Figure 4. The Sun Sparc work station in the laboratory allows the display of the small-field-of-view digital stereo images. Illustrated is a cluster of calcifications considered indeterminate on film screen images (graded as a category 4- biopsy necessary). At the work station, the 2-D DMAM images shown above may be enhance by toggling the control panel to change the magnification factor, window, level, and gamma of the images. After this post aquisition enhancement, the 2-D DMAM images were graded as a category 2; so that no biopsy would have been recommeded. The calcifications are highlighted in this example for better visualization in the stereo images. Below the 2-D DMAM stereo images the individual calcifications are shown in their segmented format prior to 3-D reconstruction.